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Febrile neutropenia in paediatric oncology

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Abstract

Febrile neutropenia (FN) is a common and dangerous consequence of myelosuppressive chemotherapy but can occur as part of the disease processes. Bacterial bloodstream infection is the most commonly diagnosed cause of febrile neutropenia, with Gram-positive organisms most frequently isolated. However, Gram-negative organisms are becoming more prevalent, with a worrying trend towards resistant organisms. When FN is prolonged, lasting for more than 5 days, there is an increased risk of invasive fungal infections. Prompt recognition, diagnosis and initiation of treatment with broad-spectrum antibiotics are essential to avoid complications and prevent rapid progression to sepsis and possible death. This short article summarises the definition, causes, pathogenesis, applied physiology and management of FN in children.

Keywords bacterial infection; bloodstream infection; chemotherapy febrile neutropenia; fungal infection; paediatric oncology

Definition

There is no international uniformly agreed definition of FN. The United Kingdom (UK) National Institute for Health and Care Excellence (NICE) defines FN as a temperature $\geq$38°C with an absolute neutrophil count (ANC) of less than 500 cells/microlitre (less than 0.5 x 10^9/L). This neutrophil cut-off was chosen because the risk of overwhelming sepsis increases as the ANC drops below 0.5 x 10^9/L. Several guidelines propose more complex definitions, for example a single fever of $\geq$38.3°C; a temperature of $\geq$38°C for more than one hour; or two episodes of fever of more than 38°C within a 12 h period. The ANC cut-off can also vary between 1.0 x 10^9/L and 0.1 x 10^9/L. Prolonged FN is neutropenia with co-existent fever lasting for more than five days, which increases the risk of invasive fungal infections.

Febrile neutropenia (FN) is most commonly encountered in the context of patients receiving myelosuppressive drugs used in the treatment of haematological and solid tumour cancers. It is the most commonly encountered complication of childhood cancer treatment, and the mortality of untreated FN is between 2 and 21%. The emergence of antibiotic resistance makes FN particularly challenging. The mortality rate in the UK more than doubled in the years between 2001 and 2010, largely due to the emergence of resistant Gram-negative organisms.

The absence of fever in a systemically unwell oncology patient should not preclude consideration of an underlying infection because the inflammatory response can be blunted, and neutropenic patients may not present with a fever despite an established infection. In particular, patients receiving high-dose steroids may have masked temperatures due to immune system suppression. Equally, febrile and systemically unwell cancer patients with a normal ANC should also be treated for serious infection because of possible qualitative immunosuppression. This is particularly true for children with haematological malignancies, as neutrophil function can be impaired even when ANC is within normal range. Cellular and humoral immunity can also be impaired, especially if neutropenia is prolonged.

Pathology, pathogenesis and applied physiology

The pathology of FN is multifactorial. Contributory factors include:

- pancytopenia
- marrow replacement
- humoral and cellular immunity qualitative defects
- mucositis
- central venous catheter (CVC) infection

Pancytopenia can be caused by the administration of cytotoxic drugs or the direct malignant invasion of bone marrow with acquired bone marrow failure. Anaemia and thrombocytopenia can be corrected with transfusion, but neutropenia in particular poses a significant danger to the patient. Neutrophils form the body's major defence against infection, particularly bacterial and fungal infection. Neutrophils phagocytose microbes and eradicate them via several methods, including production of highly toxic reactive oxygen species (ROS) in the pathogen-containing vacuole; fusion of neutrophil granules containing various antimicrobial mediators to the vacuole; and neutrophil extracellular trap formation. Neutrophils also assist in generating fevers by releasing endogenous pyrogens in response to infection, but in the absence of neutrophils, epithelial cells can release cytokines which cause fever.

In addition to direct marrow invasion, the underlying malignancy can also cause chemotactic and phagocytic defects in neutrophils which impair their ability to reach the site of infection and contain it. This is especially true for haematological malignancies.

Chemotherapy-induced mucositis causes breakdown of usual mucosal barriers in the gastrointestinal (GI) system. This allows translocation of commensal GI tract bacteria and fungi into the bloodstream, which is thought to be a major causative factor in FN caused by Gram-negative organisms.

CVCs become colonized with skin commensal bacteria and this can lead to invasive infection with these organisms. Poor CVC hygiene can also lead to infection with Gram-negative organisms, and polymicrobial infections are not uncommon.

Epidemiology

The majority of standard chemotherapy regimens used in the management of childhood cancer cause periods of myelosuppression, with neutropenia often lasting more than seven days.

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FN is most common in those children receiving chemotherapy for acute myeloid leukaemia (AML) and acute lymphoblastic leukaemia (ALL) either at initial diagnosis or relapse. More intensive regimens for solid tumours, such as high risk neuroblastoma, Ewing sarcoma, and malignant brain tumours, plus myeloablative conditioning for autologous and allogeneic haemopoietic stem cell transplantation (HSCT) are also associated with prolonged neutropenia, and an increased risk of FN.

Course of the disease

The course of an episode of FN depends upon the length of neutropenia and fever. Some patients will recover within 24—48 h of commencing broad spectrum antibiotic treatment. Prolonged FN (greater than 5 days) is associated with fungal infections, which have higher associated morbidity and mortality and are more complex to treat. The presence of significant comorbidities often also prolongs the course of the disease.

Children who do not have a documented infection 48 h after initial blood cultures were taken, who have been afebrile for more than 24 h, who are clinically stable and whose neutrophils are recovering can either be stepped down to oral antibiotics or antibiotics may be stopped altogether. Those with persistent neutropenia (neutrophil counts persistently below 0.5 x 10^9/L) can still be considered for step-down therapy if they do not have microbiologically documented infection, are clinically well, and are afebrile.

Diagnosis

History

The diagnosis of FN is made on clinical and laboratory grounds. There must be a fever and low ANC, but important additional important history points include:

- Type and duration of recent chemotherapy. Any patient who has had chemotherapy in the past 6 weeks is at risk for FN. This is especially true for myeloablative chemotherapy regimens such as those in induction treatment for acute leukaemias and post-HSCT.
- Are there localising symptoms suggesting a likely source for infection, for example cough, coryza, headache or urinary symptoms?
- Is anyone else in the family unwell? Are there known infectious contacts?
- Are there relevant underlying comorbidities, for example diabetes, lung disease, renal impairment?
- What are the current medications including prophylactic and immunosuppressant drugs.
- Document the presence of CVCs which may be a source of infection.
- Check vaccination history.
- Check for previous microbiologically-confirmed diagnoses and the patterns of resistance seen if culture results are available.

Examination

A thorough physical examination is crucial in all patients with FN, and should be repeated at least daily while the patient is unwell. A focus of infection is often not found, because the lack of neutrophils impairs the immune system's ability to produce pus, erythema, and localising pain. Therefore, regular repeated review is essential, and subtle signs should not be missed or discounted as irrelevant.

The examination should include but not be limited to:

- Vital signs (temperature, respiratory rate, blood pressure and heart rate) and assessment for haemodynamic instability.
- Oral or tympanic temperature. A rectal temperature should not be measured in oncology patients because compromised rectal mucosal integrity can induce a Gram-negative bacteraemia even with mild trauma.
- Skin signs of cellulitis, abscess or impending skin integrity breakdown, including around the CVC (if present), perineum and labial skin folds.
- Examination of the mouth for mucositis or gingivitis.
- Examine the ears, nose and throat for signs of upper respiratory tract infection, otitis media and sinusitis.
- A careful respiratory examination. Subtler signs of infection may include just an elevated respiratory rate.
- Listen to the heart sounds.
- An abdominal examination, including looking for anal fissure. Check for new hepatosplenomegaly.

Investigation

Blood cultures should always be taken from each available lumens of a CVC. Repeated blood culture sampling can be useful, especially in the case of growth of a skin commensal such as coagulase-negative Staphylococci (CoNS), as repeated growth of the same organisms is likely to reflect a true pathogen as opposed to contamination. Additional blood tests include:

- routine blood tests including full blood count, renal and liver function tests.
- markers of inflammation such as c-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and/or procalcitonin can be considered, but may be falsely reassuring.
- consider a blood gas for venous lactate if the patient is unwell to assess for sepsis

Empirical imaging for asymptomatic patient is usually not indicated, however the following modalities can be considered:

- Chest X-ray (CXR) if there are respiratory signs or symptoms, or considered if the focus of infection is unclear. CXR may not show changes if the patient is profoundly neutropenic and should be interpreted with caution. If no pathological changes are seen on CXR despite respiratory symptoms then a CT chest should be considered.
- Abdominal ultrasound can be considered after 72 h of fever, to assess whether there is fungal involvement of the kidney and/or liver

Other tests

- Perform a urine dipstick and urine culture in *all children under the age of 5 years*. Older children should have a urine sample taken if the history or examination reveals localising symptoms or underlying urinary tract abnormalities. It is important to bear in mind that neutropenic patients may not have pyuria, therefore dipstick testing or microscopy should not be used to determine whether or not to send urine samples for culture or treat empirically.

- Swabs of any inflamed or discharging skin or mucous membrane sites, especially purulent discharge, should be sent for microscopy and culture.
- Novel diagnostics including polymerase chain reaction (PCR) on blood, respiratory secretions, or other bodily fluids (apart from urine) can allow for faster diagnosis and more targeted antimicrobial therapy which may be of shorter duration.
- Diarrhoea should prompt consideration about possible typhlitis (neutropenic enterocolitis), the possibility of clostridium difficile infection (especially in HSCT patients) and Gram-negative line infection.
- The diagnosis of a fungal infection can be very difficult and investigative modalities could include abdominal ultrasound, CT chest and sinuses, bronchoscopy and alveolar lavage to identify hyphae or biopsy of suspicious lesions.

Differential diagnosis

An infectious organism is identified in only 10–40% of FN episodes. Bloodstream infection is the most common. Other sites of infection include the gastrointestinal tract (due to mucositis and translocation of bacteria), the upper and lower respiratory tract, urinary tract, skin and soft tissues.

Non-infectious causes of fever in oncology patients

It is important to consider non-infectious causes of fever particularly in children and young people who are not responding to anti-microbial treatment. Possible causes include drug fever induced by broad spectrum antibiotics and some chemotherapy drugs, tumour lysis (especially during induction chemotherapy or during the initial stages of cancer treatment); haemophagocytic lymphohistiocytosis (HLH), blood transfusion reaction, or dysautonomia with central nervous system disease involvement.

Causative organisms

FN can be caused by any community-acquired pathogen, but opportunistic infections must also be considered. Bacteria are the most common causative agent, but viral infections are also common in children. Fungal infections should be remembered in prolonged FN. It is also important to remember the possibility of other non-infectious causes of fever in patients who fail to improve on antimicrobial therapy.

Bacteria

Gram-positive cocci are the most common pathogen found in FN, especially skin commensals secondary to increased use of central venous lines and prophylactic antibiotics. Coagulase-negative Staphylococci (especially *Staphylococcus epidermidis*), *Staphylococcus aureus* and *Streptococcal* species account for 50–67% of causative organisms found. The increasing use of fluoroquinolone prophylaxis has been associated with increasing rates of selective resistance due to selective intestinal pressure. Gram-negative organisms are less common, but may lead to a more fulminant clinical course due to endotoxin and other virulence factors.

Bacterial pathogens known to cause the most serious infections are Gram-negative organisms such as *Pseudomonas aeruginosa*, and among the Gram-positive organisms *Staphylococcus aureus*, *Enterococcus* species (especially vancomycin-resistant *Enterococcus*/VRE) and *Streptococcus viridans*. Other common Gram-negative organisms include *Eschericia coli*, *Klebsiella* species, other *Pseudomonas* species, *Acinetobacter* species, and *Enterobacter* species. Polymicrobial infections are increasingly documented.

Empirical antimicrobial regimens are designed to treat both Gram-positive and Gram-negative organisms. Worryingly, the increasing prevalence of resistant Gram-negative may be increasing, leading to reduced efficacy of first-line empirical antibiotics.

Viruses

Community-acquired viral pathogens which are common to general paediatrics are also often seen in neutropenic children. Respiratory viruses commonly include Influenza, RSV, parainfluenzae, rhinovirus, adenovirus and coronaviruses. These pathogens can progress to lower respiratory tract infections more rapidly than in immunocompetent hosts, and the length and severity of illness is usually directly proportional to the duration of neutropenia.

Fungi

Fungal infections are more common in patients with profound and prolonged immunosuppression. Those children treated with myeloablative regimens, high dose steroids, prolonged neutropenia and prolonged courses of broad-spectrum antibiotics. The most common fungal pathogens are *Candida* and *Aspergillus* species. *Candida* species can translocate across the damaged intestinal wall in mucositis, with *Candida albicans* being the most common. Other candida species such as *Candida glabrata* and *Candida tropicalis* are more common in patients that have received azole prophylaxis (such as fluconazole, voriconazole or posaconazole).

With the advent of antifungal prophylaxis, which is now used widely, mould infections (most often *Aspergillus* species including *Aspergillus fumigatus*, also *Fusarium* species) are becoming more common. *Aspergillus* spores are often inhaled from the environment and mature in the upper and lower respiratory tract. CNS, bones and skin may be particularly affected by *Aspergillus*.

Endemic infections

Individuals from areas with endemic bacterial infectious diseases such as tuberculosis, and fungal infections such as *Histoplasma*, *Blastomyces* and *Coccidioides* are prone to new infection or reactivation of latent infection when receiving chemotherapy.

Post-HSCT infections

Children and young people who have undergone HSCT are at risk for all types of infection especially fungal infection given the prolonged nature of their neutropenia. They are also at risk of reactivation of certain viral infections. Clinically significant viral infections are usually reactivation of latent infection in seropositive patients with viruses such as varicella zoster virus (VZV), herpes simplex virus (HSV), Epstein–Barr virus (EBV) and cytomegalovirus (CMV). In these cases antiviral prophylaxis can be effective in avoiding severe symptoms. HSV 1 and 2 pose a risk of encephalitis. VZV can cause persistent viremia, pulmonary disease or liver failure. New infection or reactivation with the above viruses can cause significant morbidity and mortality in HSCT.

Management

FN has traditionally been treated in the inpatient setting, however more recently models of risk stratification have been developed to identify oncology patients who may benefit from outpatient treatment or early discharge for home-based treatment once stable. Risk stratification is attractive because early discharge is associated with healthcare savings and decreased rates of nosocomial infection for low risk patients.

Patients can be stratified into high and low risk FN based upon several factors including:

- the general condition of patient
- cancer type (induction ALL, infants with ALL, any child with acute myeloblastic leukaemia (AML) and any child within 30 days of HSCT are high risk)
- intensity of chemotherapy
- expected duration of neutropenia (a neutrophil count of less than 0.5 x 10^9/L for more than seven days is considered high risk)
- associated comorbidities, e.g. renal and hepatic impairment increase the risk of complications and morbidity/mortality
- any localising symptoms such as central nervous system, pulmonary, gastrointestinal (especially mucositis), CVC site symptoms such as erythema or swelling increase the risk.

The modified Alexander rule for children and young people (less than 18 years old) is a common tool used in the UK for risk assessment for septic complications. Oncology patients are considered at lower risk of septic complications unless one or more of the following conditions apply:

- treatment for AML or Burkitt lymphoma
- induction phase of treatment for ALL
- progressive disease; or treatment for relapsed disease with marrow involvement
- presenting with any of the following features:
  - hypotension
  - tachypnoea
  - hypoxia—defined as saturations less than 94% in air
  - new changes on CXR
  - altered mental status
  - severe mucositis
  - vomiting or abdominal pain
  - focal infection
- other clinical reason(s) for inpatient treatment
- neutrophil count less than 0.1 $\times$ 10^9/L

Any patients deemed to be high-risk should be treated as an inpatient. Patients considered for outpatient treatment of FN must have increasing neutrophil counts, or the duration of neutropenia is not expected to last more than seven days. Children must have stable renal and hepatic function and no significant comorbidities. They should have adequate gastrointestinal absorption and have already received a course of IV therapy (48–72 h). The family should also be readily contactable or the child have a carer who is easily contactable, live within close proximity to a medical centre (in case of deterioration), be available for daily review, and have not been receiving fluoroquinolone prophylaxis previously. The most common empiric regimen for outpatient management is oral ciprofloxacin plus amoxicillin-clavulanate.

Risk stratification may not be as effective in the teenager and young adult age group. Teenagers and young adults are often less compliant with medical treatment, and often receive higher intensity chemotherapy due to the types of cancers they are commonly diagnosed with. Research is ongoing into better methods to stratify risk in adolescents and young people, but as yet have not proved effective.

Empiric treatment of FN

Treatment should be based upon regional resistance patterns, the patient's symptoms, and previous culture results and sensitivities (both infecting and colonising organisms). First line treatment of FN is with broad spectrum antibiotics ensuring coverage of both Gram-positive and Gram-negative organisms. Monotherapy with a broad spectrum antibiotic has been shown to reduce mortality and have fewer side-effects than using two or more agents. Beta-lactam antibiotics, e.g. piperacillin-tazobactam, are recommended by NICE as first line monotherapy unless there are previous microbiological results which indicate a resistant organism. The dosage of piperacillin-tazobactam (dosed according to piperacillin component) is 90mg/kg/dose every 6 h (max per dose 4.5g).

In the case of anaphylaxis to penicillin, the patient should not have a cephalosporin or a carbapenem due to the possibility of cross reaction. These patients should be prescribed other broad spectrum agents, such as ciprofloxacin plus a glycopeptide such as vancomycin or teicoplanin.

Treatment for specific indications

CVC infection

The addition of glycopeptides, such as vancomycin or teicoplanin, is advisable in centres with high rates of MRSA colonisation. CVC removal should be considered in patients with persistent bacteraemia despite 48 h of appropriate IV therapy.

Pneumonia/CXR changes

Consider addition of a macrolide antibiotic to cover atypical organisms such as *Mycoplasma pneumoniae* (especially in school-aged children) or Legionella. A fluoroquinolone could also be considered. The possibility of *Pneumocystis jirovecii* and other fungal infections such as *Aspergillus* species must be remembered in prolonged neutropenia, especially in unwell patients.

Suspected viral infection

Patients with vesicular lesions or who are very unwell with viral symptoms should commence aciclovir.

Intra-abdominal sepsis

Beta-lactams and carbapenems provide good anaerobic organism cover, but if a patient with suspected intra-abdominal or pelvic sepsis is on any other agent, IV metronidazole should be commenced.

Skin infection

The addition of a glycopeptide to better cover skin commensal organisms may be beneficial.

Tailoring antibiotics

Patients with a microorganism confirmed infection should have their antimicrobial therapy tailored to the particular infection and antibiotic sensitivities, with duration of 7–14 days usually appropriate depending upon the organism (longer courses for Gram-negative

organisms) and neutrophil count (antimicrobials are often continued until the neutrophil count is consistently increasing).

Any patient with new clinical instability or worsening of symptoms should be urgently re-assessed, with consideration of reinvestigation and escalation of treatment. Glycopeptides and aminoglycosides are not recommended as first line therapy for FN because of side effects, and the risk of promoting emerging resistance such as vancomycin-resistant *Enterococcus*. However, they should be added if there are appropriate indications, such as suspected or confirmed MRSA for glycopeptides. An aminoglycoside such as gentamicin or amikacin can be added to treatment regimens for very unwell septic patients to cover possible resistant Gram-negative organisms.

Colony stimulating factors such as GCSF are not routinely used in the UK, but can be considered in severe prolonged neutropenia without anticipated bone marrow recovery and significant sepsis.

Suspected fungal infection

Patients who have been febrile for more than 72–96 h on antimicrobial therapy, especially those with negative blood cultures, should be investigated for fungal infection and commenced on an antifungal treatment. The most common first line antifungal drug is liposomal amphotericin B, other options include an echinocandin (e.g. micafungin), or a triazole (e.g. voriconazole). If a patient has been receiving antifungal prophylaxis prior to the episode of FN, an antifungal treatment from a different class is usually chosen as treatment. Liposomal amphotericin is usually chosen for those with renal dysfunction.

Prognosis and explanation to patient

Prognosis depends upon several factors, including clinical state at the time of presentation (those requiring intensive care with intubation and inotropic support usually have worse outcomes), organism involved (Gram-negative and fungal organisms often confer worse outcomes), and underlying malignancy (those with expected prolonged periods of neutropenia are more vulnerable to fungal infection) and complications as a result of infection.

Mortality has been reported as high as 10% in hospitalized patients, with up to 5% in those with Gram-positive infection and 18% in those with documented Gram-negative infection. Fungal infections are higher still. However, most patients recover from FN episodes without ongoing problems.

Prevention

Prophylactic antimicrobial treatment can involve administration of treatment dose antibacterial agents (often fluoroquinolones) to certain high-risk patients (AML and Down syndrome-associated leukaemia), and consideration of antifungal prophylaxis with a triazole such as itraconazole. Line care bundles involving standardized regimes around line insertion and access have been shown to reduce bacterial bloodstream infections. Gingivitis and complications from oral mucositis can be avoided with good mouth care.

The prevention of the emergence of multi-drug resistant strains (especially Gram-negative organisms) can be achieved through good prevention strategies and good antimicrobial stewardship. ◆

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Practice Points

- Febrile neutropenia is a common condition in paediatric oncology settings, especially in the induction phase of acute leukaemia and the pre-engraftment phase of allogeneic HSCT.
- Prompt recognition and diagnosis is required to prevent severe complications including death.
- Empiric therapy with broad spectrum antibiotics should be initiated quickly (60 mins from door to administration of antibiotics).
- First line treatment is usually and anti-pseudomonal beta lactam antibiotic such as piperacillin-tazobactam.
- Risk stratification can be used to guide management is used in some centres.
- Prognosis depends upon several factors including organ systems involved and severity of disease.
- The emergence of resistant Gram-negative organisms has led to an increase in mortality.